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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,454	02/15/2007	Sarman Singh	4661-0112PUS1	4159

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BIRCH STEWART KOLASCH & BIRCH  
PO BOX 747  
FALLS CHURCH, VA 22040-0747

EXAMINER
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WILDER, CYNTHIA B

ART UNIT	PAPER NUMBER
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1637

NOTIFICATION DATE	DELIVERY MODE
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05/27/2010

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/584,454	<b>Applicant(s)</b> SINGH, SARMAN	
	<b>Examiner</b> CYNTHIA B. WILDER	<b>Art Unit</b> 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 3/17/2010.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☐ Claim(s) 1-9 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 2-8 is/are allowed.
- 6) ☒ Claim(s) 1 and 9 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 June 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)                        | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. Applicant's amendment filed 3/17/2010 is acknowledged and has been entered. Claims 1-2 and 9 have been amended. Claims 1-9 are pending. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

**This action is made FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### **Previous Rejections**

3. The prior art rejections under 35 USC 103(a) direct to claims 1 and 9 are maintained and discussed below.

### ***Claim Rejections - 35 USC § 103***

4. Claims 1 and 9 finally are rejected under 35 U.S.C. 103(a) as being unpatentable over Salotra et al (20030162182, August 28, 2003, filing date February 2002) in view of Reed et al (WO 9416331, July 1994) in view of Lowe et al and further in view of Belli et al (Am. J. Trop. Med. Hyg. Vol. 58, no. 1, pages 102-109, 1998). Regarding claims 1 and 9, Salotra teach a primers and a kit for amplification and detection of kinesin related gene of Leishmania species in a sample, the method comprising the steps of (a) isolating DNA from a sample; (b) amplifying a target region from the DNA of step (a) using isolated primer sequences and heat stable DNA polymerase to obtain amplified fragments, (c) separating the amplified fragments of step (b); and (d) analyzing the

fragment of step (c) to detect and characterize *Leishmania* species based on a banding pattern of the amplified fragments following electrophoresis (0025-0031 and 0038, see also Table 1 which gives results of PCR assay in KA and PKDL clinical samples and control; see also 0034 which teaches the concept of a kit comprising reagents for performing the method. It is noted that the presence of an instruction manual is deemed inherent in the kit. Further MPEP states, "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, >367 F.3d 1336,1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004))".

Salotra et al differs from the instant invention in that the reference does not teach the primer sequences consisting essentially of the sequences of SEQ ID NOS: 1-4 or wherein the primers are all used in a single polymerase chain reaction. However methods of isolating and designing sequences from a larger gene sequence is well known in the art. For example, Reed et al teach a nucleic acid sequence of *Leishmania* comprising a sequence substantially identical to the sequence of *SEQ ID NO: 1* (see page 17, SEQ ID NO: 2 which teaches a sequence 100% identical to SEQ ID NO: 1 at nucleotide position 2681 to 2697) (see alignment below);

SEQ ID NO: 1	1	CTAGAGCAGCAGCTTCG	17
Reed et al	2681	CTAGAGCAGCAGCTTCG	2697
SEQ ID NO: 2			

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SEQ ID NO: 2 (see page 17, SEQ ID NO: 2 which teaches a sequence 100% identical to the sequence of SEQ ID NO: 2 at nucleotide position 2564 to 2580) (see alignment below);

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SEQ ID NO: 2           1 CTTGAGCAGCAGCTTCG 17
                        |||
Reed et al           2564 CTTGAGCAGCAGCTTCG 2580
SEQ ID NO: 2

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SEQ ID NO: 3 (see page 17, SEQ ID NO: 2 which teaches a complement sequence that is 100% identical to the sequence of SEQ ID NO: 3 at nucleotide positions 2797 to 2781) (see alignment below);

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SEQ ID NO: 3           1 CGTGGCCCTCGTGTCT 17
                        |||
Reed et al           2797 CGTGGCCCTCGTGTCT 2781
SEQ ID NO: 2

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and SEQ ID NO: 4 (see page 17, SEQ ID NO: 2 which teaches a complement sequence 82.4% identical to the sequence of SEQ ID NO: 4 at nucleotide positions 3265 to 3252) (see alignment below).

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SEQ ID NO: 4           1 CGCGGCCCTCGTGT 14
                        |||
Reed et al           3265 CGCGGCCCTCGTGT 3252
SEQ ID NO: 2

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Lowe et al teach a method for designing primers and evaluating their performance wherein Lowe et al disclose a computer program for rapid selection of oligonucleotide primers for polymerase chain reaction (see page 1757, col. 1, abstract). Lowe et al. teach that all primers designed for over 10 gene products were experimentally tested and the results showed that all the amplification products

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specified by the primers are of the predicted size and also hybridize with the appropriate cDNA or internal oligonucleotide probe (see page 1760, col. 2, paragraph 1).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made, to combine the known nucleic acid sequence as taught by Reed with a step of generating primers and designing primers as taught by Lowe et al. to amplify and to detect kinesin related genes of Leishmania species as suggested by Salotra et al.

The ordinary artisan would have a reasonable expectation of success that such primers generated using known sequences as taught by Reed and Salotra et al. in view of Lowe et al. would amplify or detection Leishmania species because the claimed primers are functional equivalents of the sequences taught by Salotra et al and further because Lowe et al. explicitly teaches that all primers designed for over 10 gene products were experimentally tested and the results showed that all the amplification products specified by the primers are of the predicted size (see page 1760, col. 2, paragraph 1).

The ordinary artisan would have been motivated to generate a number of said primers for detecting Leishmania species and place them in the form of a kit. Such primers are considered functionally equivalent to the claimed primers of the instant invention. Further, selection of specific oligonucleotides for specific T<sub>m</sub> represents routine optimization with regard to sequence, length and composition of the oligonucleotide, which routine optimization parameters are explicitly recognized in Lowe et al. (This clearly shows that every primer would have a reasonable expectation of

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success). As noted in *In re Aller*, 105 USPQ 233 at 235, more particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Routine optimization is not considered inventive and no evidence has been presented that the primer selection of Salotra was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Salotra et al in view of Reed et al do not expressly teach wherein multiple primers are used in the same PCR assay. However, the concept of using multiple primers in a multiplex PCR based assay is well known in the art.

For example, Belli et al teach a multiplex PCR reaction using multiple primers that allows simultaneous detection of the Leishmania genus (abstract and page 103, section entitled "Polymerase chain reaction amplification"). Belli et al teach that the multiplex reaction minimizes the number of PCRs necessary to characterize the Leishmania strains (see page 4, col. 2, last paragraph). Belli et al teaches that PCR offers certain advantages over classic techniques for diagnosis and characterization of infectious pathogens. Belli et al teach when appropriately applied, the PCR can be more specific, sensitive, versatile, and rapid than conventional methods; in addition, genetic information can be obtained in the process (last paragraph, col. 2, page 106). Belli et al teaches that PCR is particularly useful in case of leishmaniasis, due to the requirement for parasitologic confirmation and to the limitations of classic methodologies (page 107, col. 1, second paragraph).

Therefore, it would additionally have been *prima facie* obvious for one of ordinary skill in the art at the time of the claimed invention to have been motivated to have modified the amplification reaction of Salotra et al in view of Reed et al and Lowe et al to encompass a PCR reaction comprising the use of multiple primers in a multiplex reaction as taught by Belli et al. One of ordinary skill in the art at the time of the claimed invention would have been motivated to do for the advantages of reducing the number of PCRs necessary to characterize Leishmania strains and to increase specificity, sensitivity and versatility of detection as taught by Belli.

### ***Response to Arguments***

6. Applicant traverses the rejection on the following grounds: Applicant states that the Examiner has fallen a victim to hindsight using the disclosure of the present application to select from the very long gene sequence presented in the cited references those few contiguous base pairs constituting the oligonucleotide primer recited in the instant claims. Applicant cites case law and states that the specification provides evidence of unobviousness of the claimed invention. Applicant states that the present invention provides tools to accurately diagnose infection with strains of Leishmania that cause either visceral or cutaneous disease. Applicant states that the combined references do not provide such tools. Applicant states that Salotra relied upon by the Examiner shows a positive indication of both KA and PKDL strains using the primer set Ld1. Applicant further states that the primer set of the present invention allows the clinical practitioner to distinguish infection by VL or by PKDL strains.

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Applicant states that the above-explained results can be applied either to assert that the cited combination of references fail to establish any expectation success in making the present invention or as evidence of results unexpected by one of ordinary skill in the art obtained by the invention.

7. All of the arguments have been thoroughly reviewed and considered but is not found persuasive for the reasons that follow: While the examiner acknowledges Applicant's arguments, it is noted that the selection and designs of primer sequences for detecting a specific target is well known in the prior art, when the gene from which the primers have been isolated is known. Applicant is again reminded that the prior art of Salotra et al and Lowe and Reed et al had already taught the ordinary artisan to target the minicircle region conserved in all strains of *Leishmania* to detect different strains of *Leishmania* (see Belli, page 103; see Salotra et al which teaches primer designed for use in the method based on the donovani kinetoplast mini-circle sequence (see page 850, col. 2, section entitled "oligonucleotide primers")). Likewise, methods for aligning known nucleic acid sequences to arrive at primer and probe combinations are well-known and commonly applied in the prior art as taught by the cited references. For example, Salotra and especially Lowe et al provides evidence of selecting and/or designing primers from a larger known sequence. Thus, contrary to Applicant's arguments in this case, it is not unpredictable to design the primers and primers and claimed in the instant invention because the cited prior art has already given the ordinary artisan the necessary tools to design primer and probe to target gene sequences from *Leishmania*.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, the Examiner maintains that it is within the ordinary artisan's capability to obtain primer sequences from a longer sequence of a known gene with a reasonable expectation of success as software, databases and computer programs provide sufficient means of designing and selecting primer sequences for detecting a desired target.

In response to Applicant's arguments concerning unexpected results, Applicant provides no evidence to support this conclusion. MPEP states that "objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

In response to Applicant's arguments concerning the advantages of the instant invention, it is noted that Applicant's arguments are not commensurate in scope with the

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claims as currently written. The claims 1 and 9 are not drawn to a method comprising specific method steps, but a product comprising oligonucleotides and reagents for kit. MPEP states "the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In this case, this is particularly true because the prior art provides sufficient evidence that it would be obvious to select a combination of primers and place them in a kit for use in PCR type reactions. Applicant's arguments are not sufficient to overcome the prior art rejections directed to claims 1 and 9.

### ***Conclusion***

8. Claims 1-9 are rejected. Claims 2-8 contain allowable subject matter for reasons made of record in the prior Office action. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GARY BENZION/

Supervisory Patent Examiner, Art Unit 1637